4. INFORMATION CONCERNING ULTRAVIOLET A (UVA) RADIATION TESTING AND LABELING OF OTC SUNSCREEN DRUG PRODUCTS (FROM THE ABOVE MENTIONED JANUARY 27TH AND OCTOBER 26TH MEETINGS AND JULY 16TH LETTER):

a) Explain the rationale concerning the selection of the "critical wavelength" method over other *in vitro* UVA test methods (including the Diffey "ratio" method).

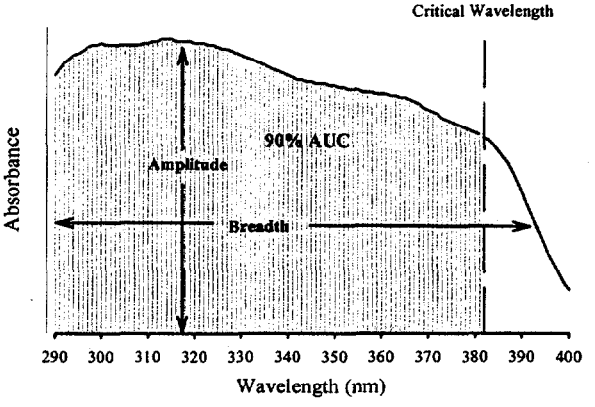
Comment

The rationale for selecting the "critical wavelength" to evaluate UVA protection over other *in vitro* tests is that it provides a simple, reproducible and adaptable method which can account for sunscreen product photostability, and is independent of SPF yet ensures UVA protection commensurate with SPF. Further, based on our extensive evaluation of the suncare market[8], the critical wavelength method is accurate and sensitive, distinguishing products containing established long wave UVA filters[9] from those that do not or contain insufficient amounts. What is most important is that the critical wavelength provides an understandable and accurate approach from which a transparent and explicit label may be determined for communicating broad-spectrum photoprotection to the consumer.

To more completely address this question, we have broken it into two parts: (1) what is the critical wavelength method, and (2) what advantages does it [critical wavelength] have over other *in vitro* methods.

(1) What is the Critical Wavelength Method?

In 1994, Diffey[10] described the Critical Wavelength method which is based on the absorption spectrum of a sunscreen product obtained using UV substrate spectrophotometry and illustrated in the following figure.



[8]Aug. 1997 letter/report from Procter & Gamble Co. to FDA entitled "Assessment of appropriateness and practical utility of *in vitro* critical wavelength determination procedure for the broad-spectrum classification of sunscreen products. Diffey, BL, Tanner, PR, Matts, PJ, Nash JF (2000) In vitro assessment of the broad-spectrum ultraviolet protection of sunscreen products. *J Am Acad Dermatol*, in press.

[9] Federal Register (1996) Sept. 16, **61** FR 48645; Federal Register (1998) Oct. 22, **63** FR 56584

[10] Diffey BL. (1994) A method for broad-spectrum classification of sunscreens. *Int J Cosmet Sci*, **16**:47-52.

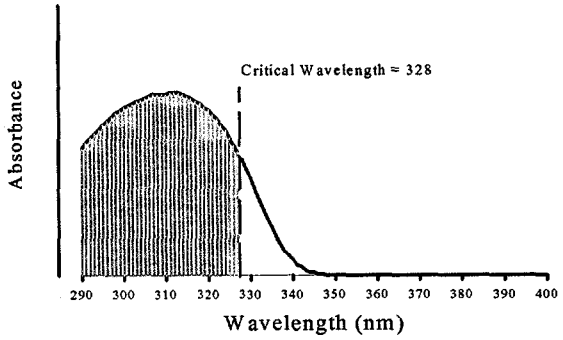
The absorption spectrum is reduced to a single index termed **Critical Wavelength, sometimes abbreviated** λ_c; the value is defined as the wavelength where the integral of the spectral absorbance curve reached 90% of the integral from 290 to 400 nm. It is calculated using the following equation:

$$\int_{290}^{\lambda_c} A(\lambda)d\lambda = 0.9 \int_{290}^{400} A(\lambda)d\lambda$$

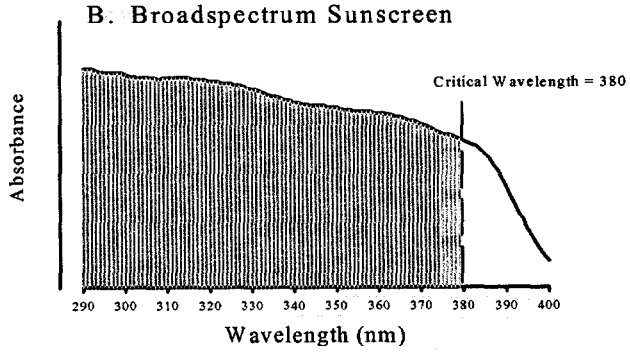
The critical wavelength value is based on the inherent shape of the absorbance curve not its amplitude and, therefore, is independent of application thickness and other undesirable variables characteristic of *in vitro* calculations of absolute protection factors. This method makes no assumptions regarding the action spectra for UVA-induced acute or chronic skin effects and obviates the need for human subjects utilizing clinical endpoints with indeterminate value in relation to protection from sunlight. The critical wavelength is independent and complimentary to SPF, and when considered together a complete description of sunscreen product efficacy is provided. Thus ***in vivo* SPF (Amplitude) + Critical Wavelength (Breadth) =Full Spectrum (UVA + UVB) Sunscreen product efficacy.**

Examples of the critical wavelength determination are illustrated in the following figures. The shaded areas in A and B represent 90% of the area-under-the-absorption curve from 290 to 400 nm. The critical wavelength for a "UVB sunscreen" (Fig A) is less than that of a "Broadspectrum Sunscreen" (Fig B).

A. UVB Sunscreen



B. Broadspectrum Sunscreen



(2) What advantages does it [critical wavelength] have over other in vitro methods.

Absorbance curves generated from *in vitro* substrate spectrophotometric measures of sunscreen products may be used to calculate any number of endpoints including, UVA protection factors such as PFA or persistent pigment darkening (PPD) using proposed action spectra, ratios of UVA/UVB as well as critical wavelength.

The calculation of *in vitro* UVA "protection factors" (PFA, PPD, etc.) depend on the amplitude of the absorbance curve which is a function of extinction coefficients and application thickness. Because the amplitude of the absorbance curve is highly variable, the calculated protection factors are, in general, not predictive of actual *in vivo* performance which is why the SPF calculated *in vitro* may not agree with the *in vivo* measure[11]. As well, *in vitro* calculation of UVA protection factors requires convolution with existing or proposed action spectra for the endpoint measure which introduces variability and arguably indeterminate biological meaning since existing endpoints such as persistent pigment darkening (PPD) are not a surrogate for the endpoints of concern, namely photoaging and photocarcinogenesis. Finally, in at least one study, the *in vitro* UVA protection factors calculated for 36 sunscreen products were reported to correlate with SPF[12] and, as such were considered to be of limited value, providing little information beyond that of the SPF itself.

To minimize the problems associated with the generation of protection factors, Diffey proposed a UVA/UVB ratio as a measure of UVA protection. This ratio of UVA/UVB absorbance was adopted by Boots the Chemist in the UK and is used to define the star rating system[13]. This method of defining UVA protection gives an indication of the physical properties, i.e., absorbance, of a sunscreen product independent of concentration and application thickness. However, there are at least two concerns regarding any ratio method:

- the ratio propagates the arbitrary, anthropogenic distinction between UVA and UVB. (Consumers are exposed to the whole UV spectrum from sunlight not just an artificially defined band of UV.); and,
- the ratio can be manipulated by increasing short wavelength UVAII protection (i.e., 320-340 nm) without providing long wavelength UVAI protection.

Because of these shortcomings, Prof. Diffey proposed the Critical Wavelength method[6]. As described in detail in the preceding section, the determination of this singular, summary statistic depends only on extinction coefficients of the sunscreen active ingredients and therefore provides a reproducible index of the breadth of UV protection which is independent of SPF. **As such, this is the recommended method to evaluate long wave efficacy of sunscreen products.**

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[11] Sayre, RM, Agin PP, LeVess GL, Marlowe E. (1979) A comparison of *in vivo* and *in vitro* testing of sunscreening formulas. *Photochem. Photobiol.* **29**:559-66. Brown S, Diffey BL (1986) The effect of applied thickness on sunscreen protection: *in vivo* and *in vitro* studies. *Photochem. Photobiol.* **44**:509-13.

[12] Diffey, BL (1997) Indices of protection from in vitro assay of sunscreens. In Sunscreens. Development, evaluation, and regulatory aspects. Lowe, NJ, Shaath, NA and Pathak, MA (eds.), pp 589-599, Marcel Dekker.

[13] Boots the Chemist Ltd. *The guide to practical measurement of UVA/UVB ratios.* The Boots Co. PLC, Nottingham, England. Diffey, BL, Robson, JA (1989) A new substrate to measure sunscreen protection factors throughout the ultraviolet spectrum. *J Soc Cosmet Chem* **40**:127-133.